
GENERAL REVIEW AND ENFORCEMENT POLICIES

IMPLEMENTATION OF CAUSAL REVIEWS

A causal review of an approved NADA involves the re-evaluation of basic animal safety and efficacy data, manufacturing methods and controls or human food safety data. It is initiated on a problem-oriented basis when information identifies a possible safety or effectiveness problem that may be severe enough to support withdrawal of the NADA under Section 512(e) of the Act.

The marketing history of each approved NADA will be reviewed at least once a year following receipt of the annual Drug Experience Report (DER). There is also an ongoing review of the literature relating to human safety data. If the DER review, or supplemental NADA review, or other information indicates that a serious problem exists, problem-solving procedures will be implemented. Among these is the review of safety and efficacy data in the associated NADAs. Since such reviews will be performed only on a problem-oriented basis, they are appropriately termed causal reviews. Such reviews will not be used simply to update the safety or efficacy data in NADAs to current standards where no problem of safety or efficacy exists. While causal reviews are initiated by and performed on a specific problem-oriented basis, the resolution of the problem(s) may directly affect other safety and efficacy components of the approved NADA. The final recommendation should be based on a complete and thorough review of all pertinent information, and may not be limited to the particular problem area which initiated the review, if other safety and efficacy components of the NADA are directly affected.

The basic purpose of a causal review is to clarify and to resolve an identified problem. The purpose of the review is not to ensure that each study in an NADA meets every current standard for such studies but rather to establish that sufficient data derived from adequate and well-controlled studies exist upon which a sound regulatory decision can be based in order to resolve the problem. Or, in statutory terms, that existing data evaluated in light of new information demonstrate that a product or class of products is both safe and effective under the conditions of use established in the labeling.

Although the decision by HFV-100, HFV-200, and HFV-1 to begin a particular causal review may be judgmental, we can be guided effectively by the continuing review of marketed new animal drugs under the DER system and the routine screening of this and other sources of human safety data. Similar or related NADAs may be included in any re-evaluation unless it is clear that the problem is product (or formulation) specific.

Before NADAs are considered to be subjects of a causal review, the action will be approved in writing by the Office Directors for New Animal Drug Evaluation (NADE), Surveillance and Compliance (S&C), and the Center Director. Priorities for these causal reviews will be established at that time based on the seriousness of the problem.

I. Purpose:

For a number of years, CVM has performed re-evaluations of safety and effectiveness data in NADAs on the basis of new information that identifies a problem. Such reviews are essential to determine whether any of the conditions of 512(e) of the Federal Food, Drug, and Cosmetic Act are applicable to the situation and to determine the most appropriate course of action to resolve the problem. Such reviews were generally referred to within the Center (then Bureau) as "in-depth" reviews. These reviews will continue to be performed to satisfy the requirements of 512(e).

Most frequently decisions to initiate such reviews are based on the continuing submission of reports of adverse drug reactions which involve only one or a limited number of products, usually manufactured by one firm. Many of these problems can be most effectively resolved by dealing directly with individual firms on an ad hoc basis.

However, a number of situations arise in which new information may indicate that a problem involves more than one drug product and/or sponsor. The issues may be serious and difficult to resolve. Formal administrative procedures to address such situations and to prioritize and coordinate such activities on a more formal basis are essential for effective use of manpower. Thus, in 1979, procedures to provide for more efficient handling of these situations were first placed in the Policy and Procedures Manual of the Center. These have since been revised and updated.

These procedures are not the only mechanism by which the Center resolves problems under the authority of 512(e), rather they represent the most formal and complex of a broad range of activities to ensure the continued safety and effectiveness of approved new animal drugs.

The ongoing process represented by these causal review procedures provides a systematic method of re-evaluating safety and effectiveness data when a problem is identified relating to the use of a marketed new animal drug. This systematic re-evaluation permits the Agency to approve many supplemental NADAs without re-evaluating the underlying safety and effectiveness data each time a supplement is submitted, or in other cases, to limit the re-evaluation to that portion of the underlying data directly applicable to the purpose of the supplement.

II. Procedure:

- A. Any group in CVM which identifies a need for a comprehensive review of underlying data in an NADA (or group of NADAs) based on information which indicates that a significant problem exists, may recommend the implementation of a causal review.
- B. The recommendation should be in the form of an action memo providing background information on how the problem was identified, the severity and scope of the problem, and the relative need for timely resolution (i.e., the priority relative to other ongoing CVM activities). The memo should be directed for concurrence through the supervisory chain including Office Directors for NADE and S&C to the Center Director.
- C. If the recommendation is accepted, the Division of Epidemiology and Surveillance (for reviews initiated due to animal safety and efficacy problems) or the Office of Director for NADE (for reviews initiated due to human food safety problems), will prepare a memorandum for distribution to all Division Directors and the Supervisor, Document Control Unit (DCU). The memo will contain:
 - 1. Background information on the history, discovery, severity and priority of the problem.
 - 2. Instructions to division(s) with supplements under review to:
 - a. Expedite completion of Category #1 supplements and those Category #2 supplements which can be reviewed without reference to underlying safety and effectiveness data.
 - b. Discontinue review of those Category #2 supplements which cannot be reviewed without reference to the underlying safety and effectiveness data because such data will be subject to the causal review.
 - 3. Instructions to DCU to expeditiously forward all files, jackets, and unfiled material to the appropriate causal review group.
- D. Once the files have been forwarded, incoming Category #1 supplements and those Category #2 supplements which can be approved without reference to underlying safety and effectiveness data should be processed in a manner which does not impede the causal review.
- E. Category #2 supplements involving, e.g., alterations of dose (including dosage regimen) and/or the addition of claims for the same target species will not usually be

approvable while a causal review is ongoing. Approval of these supplements will normally require a re-evaluation of the underlying safety and effectiveness data which would interfere with the causal review.

- F. The Division of Epidemiology and Surveillance (for animal safety or efficacy problems) or the Office of the Director for NADE (for human safety problems) will send a letter, signed by the appropriate Office Director, to the involved firm(s) telling them that their NADAs have been identified for a causal review. This letter will identify the problem, request any additional data not previously submitted, indicate the impact the action will have on related supplemental NADAs, and give the firm(s) 30 days to respond. The response should be directed to the appropriate causal review group.
- G. The Division of Epidemiology and Surveillance (DES) will perform all reviews of animal safety and efficacy or manufacturing methods and control data but normally will not duplicate a recent scientific review already completed by NADE. DES will perform all administrative work associated with reviews initiated as a result of animal safety or efficacy problems. NADE will perform reviews relative to human food safety. The Office of the Director for NADE will administer such reviews.
- H. Following review of the NADAs, the group with administrative control, will prepare for distribution to the Office Directors a summary of all findings and a list of recommendations. The recommendations may be, but are not necessarily limited to, one of the following:
 - 1. The product is unsafe or ineffective, or has not been shown to be safe or effective, and a 512(e) withdrawal should be initiated. The firm(s) will be notified by letter, and a Notice of Opportunity for Hearing (NOOH) will be initiated unless the firm(s) voluntarily withdraw the NADA(s).
 - 2. There is significant cause for concern regarding the safety and/or effectiveness of the product but the problem is of such a nature that the firm(s) can be given time to generate the needed data. No immediate administrative action should be taken against the NADA. The products should be allowed to remain on the market while the data are developed. The firm(s) will be required to meet specific time frames involving all phases of data generation. Withdrawal will proceed unless needed data are generated within the specified time frames.
 - 3. The specific problem has been identified and may be corrected, without further studies, by formulation changes, manufacturing and/or

label changes, use of additional warning statements, altered withdrawal time, changing from over-the-counter to prescription use, or other similar changes. Time frames will be imposed for all changes required of the firm(s). Withdrawal will proceed unless changes are made within the specified time frames.

- I. The letter that is issued to the involved sponsors following a causal review will be regulatory in nature. It will identify specific data deficiencies and/or changes required in the product or its labeling which if not corrected within a specific time will result in the initiation of withdrawal proceedings under 512(e) of the Act. Other deficiencies noted during the review, but not sufficient to support withdrawal of the NADA, may be identified in an "informal" part of the letter with the understanding that data submission or changes are requested but not required.